## WORLD INTELLECTUAL PROPERTY ORGANIZATION



### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: **WO 99/65469** (11) International Publication Number: **A3** A61K 9/16, 9/51, 9/14 (43) International Publication Date: 23 December 1999 (23.12.99)

PCT/US99/13755 (21) International Application Number:

(22) International Filing Date: 18 June 1999 (18.06.99)

(30) Priority Data:

19 June 1998 (19.06.98) 60/089,852

US

(71) Applicant: RTP PHARMA INC. [CA/US]; 4364 South Alston Avenue, Durham, NC 27713-2280 (US).

(72) Inventors: PACE, Gary, W.; 6913 Hunters Way, Raleigh, NC 27615 (US). VACHON, G., Michael; 445, rue Strathcona, Westmount, Quebec H3Y 2X2 (CA). MISHRA, Published K., Awadhesh; Appartement 201, 670 de Gaspe, Iles des Soeurs, Verdun, Quebec H3E 1H8 (CA). HENRIKSEN, Inge, B.; Lagaardsvegen 131, N-4010 Stavanger (NO). KRUKONIS, Val; 287 Emersion Road, Lexington, MA 02173 (US). GODINAS, Anthony; 30 Washington Street, Methuen, MA 01844 (US).

(74) Agent: CRAWFORD, Arthur, R.; Nixon & Vanderhye P.C., 8th floor, 1100 North Glebe Road, Arlington, VA 22201-4714 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, JA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM; GA, GN, GW, ML, MR, NE, SN, TD, TG).

With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 2 March 2000 (02.03.00)

#### (54) Title: PROCESSES TO GENERATE SUBMICRON PARTICLES OF WATER-INSOLUBLE COMPOUNDS

#### (57) Abstract

Submicron particles of water-insoluble compounds, particularly drugs, are prepared by simultaneously stabilizing microparticulate suspensions of same with surface modifier molecules by rapid expansion into an aqueous medium from a compressed solution of the compound and surface modifiers in a liquefied gas and optionally homogenizing the aqueous suspension thus formed with a high pressure homogenizer.

### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia	
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia	
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal	
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland	
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad	
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo	
ВВ	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan	
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan	
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey	
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago	
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine	
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda	
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America	
CA.	Canada	iT	Italy	MX	Mexico	UZ	Uzbekistan	
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam	
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia	
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe	
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand			
CM	Cameroon		Republic of Korea	PL	Poland			
CN	China	KR	Republic of Korea	PT	Portugal	•		
CU	Cuba	KZ	Kazakstan	RO	Romania			
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation			
DE	Germany	Li	Liechtenstein	SD	Sudan			
DK	Denmark	LK	Sri Lanka	SE	Sweden			
EE	Estonia	LR	Liberia	SG	Singapore			

### INTERNATIONAL SEARCH REPORT

Inte onal Application No PCT/US 99/13755

A. CLASSI IPC 6	FICATION OF SUBJECT MATTER A61K9/16 A61K9/51 A61K9/14	4	
According to	o International Patent Classification (IPC) or to both national classific	ation and IPC	
B. FIELDS	SEARCHED		<del>-</del>
Minimum do	ocumentation searched (classification system followed by classification $A61K$	ion symbols)	
Documenta	tion searched other than minimum documentation to the extent that s	such documents are included in the fields se	earched
	lata base consulted during the international search (name of data ba	ise and, where practical, search terms used	)
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the rel	evant passages	Relevant to claim No.
E	WO 99 52504 A (HOFFMANN LA ROCHE) 21 October 1999 (1999-10-21) the whole document	)	1-16
А	WO 97 14407 A (RES TRIANGLE PHARMACEUTICALS ;UNIV TEXAS (US) HENRIKSEN INGE B (U) 24 April 1997 (1997-04-24) cited in the application the whole document	;	1–16
А	WO 95 21688 A (WEIDNER ECKHARD ; F ZELJKO (SI); NOVAK ZORAN (SI)) 17 August 1995 (1995-08-17)	KNEZ	
А	US 3 998 753 A (ANTOSHKIW THOMAS ET AL) 21 December 1976 (1976-12-		
		-/	
X Fun	her documents are listed in the continuation of box C.	χ Patent family members are listed	in annex.
* Special ca	ategories of cited documents :	"T" later document published after the inte	mational filing date
consid	ent defining the general state of the art which is not dered to be of particular relevance	or priority date and not in conflict with cited to understand the principle or the invention	the application but
filing o		"X" document of particular relevance; the cannot be considered novel or cannot	be considered to
which	ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another n or other special reason (as specified)	"Y" document of particular relevance; the c cannot be considered to involve an in	taimed invention ventive step when the
other	ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but	document is combined with one or mo ments, such combination being obvior in the art.	ore other such docu-
later ti	han the priority date claimed	"&" document member of the same patent	
	actual completion of the international search  23 December 1999	Date of mailing of the international set	агсн героп
Name and	mailing address of the ISA	Authorized officer	
	European Patent Office, P.B. 5818 Patentlaan 2		•
	NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Fischer, W	

2

# INTERNATIONAL SEARCH REPORT

Int ional Application No PCT/US 99/13755

		PCT/US 99	7/13/55		
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT					
Category "	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.		
A	G. DONSI ET AL.: "POSSIBILITY OF APPLICATION TO PHARMACEUTICAL FIELD" PHARM. ACTA HELV,1991 - 1991, pages 170-173, XP002900588				
	`				
	·				

# INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inte :onal Application No PCT/US 99/13755

Patent document cited in search report		t	Publication Patent family date member(s)		Publication date	
WO	9952504	Α	21-10-1999	NONE		
WO	9714407	Α	24-04-1997	AU AU EP	709262 B 7461796 A 0855906 A	26-08-1999 07-05-1997 05-08-1998
WO	9521688	A	17-08-1995	SI AT CA DE DK EP ES GR JP	9400079 A 159184 T 2182786 A 59500808 D 744992 T 0744992 A 2109095 T 3025495 T 9508851 T	31-10-1995 15-11-1997 17-08-1995 20-11-1997 02-06-1998 04-12-1996 01-01-1998 27-02-1998 09-09-1997
US	3998753	Α	21-12-1976	AT AT BE DE FR GB IT JP NL	351912 B 625675 A 832331 A 2534091 A 2281961 A 1502895 A 1050722 B 51041732 A 7509586 A	27-08-1979 15-01-1979 12-02-1976 26-02-1976 12-03-1976 08-03-1978 20-03-1981 08-04-1976 17-02-1976